

Mechanisms of Cancer-Induced Bone Pain

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Abstract: Bone is a common site of advanced cancer metastasis, second only to the lungs and liver. Cancer-induced bone pain (CIBP) is a persistent and intense pain that is caused by a combination of inflammatory and neuropathic factors. As CIBP progresses, the degree of pain intensifies. Despite advancements in medical technology, the treatment outcomes of patients with CIBP remain unsatisfactory, and severe pain can typically only be controlled with opioid medications. However, patients treated with opioid medications often develop tolerance. Therefore, they may require dose increases, which can increase the severity of opioid-induced side effects, in turn influencing quality of life. The peripheral mechanisms of CIBP primarily involve bone tissue damage, tumor microenvironment formation, and changes in the dorsal root ganglion. The central mechanisms usually involve biochemical and electrophysiological changes in the spinal cord and brain. The spinal cord is the main processing center for nociceptive signals. When tumor cells produce inflammatory mediators that acidify the microenvironment or damage nerve endings, the spinal cord becomes excessively stimulated, resulting in increased or prolonged pain signals that propagate to the higher central nervous system through the ascending pathway. There are substantial differences in the pain generation mechanisms between CIBP and common inflammatory and neuropathic pain. Therefore, understanding the mechanisms underpinning CIBP development at the level of the spinal cord is crucial for optimizing pain management. This study explores the pathogenesis of CIBP at the level of the spinal cord and describes recently proposed treatment methods for CIBP.

Keywords: Cancer-induced bone pain, spinal cord, microglia, neuron, astrocyte

Introduction

Bone is a common site of metastasis for many malignant tumors. Tumor cells colonize in the vascular microenvironment of the bone marrow, supporting cell growth, metastasis,¹ tumor growth, and invasion.² Some types of cancer are prone to bone metastasis, including breast cancer, especially estrogen receptor-positive breast cancer, and prostate cancer, for which the incidence of bone metastasis is 53.71% and 88.74%, respectively.³ Other types of cancer that are prone to bone metastasis include thyroid, kidney, lung and bladder cancer, for which the incidence of bone metastasis is reported to be 20.29%, 38.65%, 36.86% and 31.08%, respectively.³

With medical advances, the survival time of patients with tumors has increased, however, the phenomenon of bone metastasis is also increasing. Bone metastasis can lead to pain, pathological fractures, and other manifestations, which cause patients to experience severe pain. Moreover, once tumors have metastasized to bone, they are generally incurable. Therefore, current treatment methods are mainly palliative, including acupuncture, opioids and analgesics, radiotherapy, and behavioral therapies. Radiotherapy and behavioral therapy, aim to reduce patients suffering and improve quality of life.⁴

Cancer induced bone pain (CIBP) is a complex type of pain induced by primary bone tumors or bone metastases in patients with advanced cancer. Owing to its unstable onset time and severity, CIBP seriously affects the quality of life of affected individuals. With the development of medical technology, the survival time of patients with CIBP is gradually increasing. However, the incidence of CIBP is also increasing, and according to a previous study, 31.8% of patients with cancer are still undertreated.⁵

CIBP is a complex pain state with a multifactorial pathogenesis that involves inflammation, neuropathic processes and tumor specific mechanisms. The peripheral mechanisms of CIBP mainly involve interactions between bone cells, tumor cells, immune cells, and nerve fibers in the tumor microenvironment. These peripheral mechanisms can lead to central nervous system (CNS) excitability activation, driving neurons in the brain and spinal cord to adopt a hypersensitivity state. This is accompanied by a series of biochemical reactions in the microglia, astrocyte, and immune cells. Collectively, these pathological changes lead to the sensation of pain.^{6,7}

The spinal cord is the main pathway for information exchange between the brain and peripheral nerve fibers.⁸ Most of the sensory fibers from the dorsal root ganglion (DRG) pass through the dorsal root and converge in the dorsal root entry zone. The dorsal horn of the spinal cord is the first level of modulation for nociceptive conduction. Destruction of the dorsal horn may destroy the central part of the posterior spinal root, Lissauer's bundle, and the neurons of layers I–IV of the posterior horn of the spinal cord, eliminating the production and conduction of pain signals in this area, thus achieving pain relief. The dorsal horn of the spinal cord is a major site involved in the regulation of upward and downward pain pathways, with the majority of A δ and C fibers terminating in laminae I–II, and A β fibers projecting to laminae III–IV. Neurons with a wide dynamic range are distributed throughout the dorsal horn of the spinal cord, but they are predominantly present in lamina V, which receives both injurious and non-injurious sensory information as well as sensory inputs from visceral and somatic sources. Enthesopathy is the phenomenon of convergence of visceral and somatic sensations.

In patients with CIBP, noxious stimuli are transmitted to the brain via the spinal cord. The stimulated nerves tend to undergo specific changes at the level of the spinal cord, which in turn affects the overall environment within the spinal cord. Therefore, understanding how the spinal cord integrates the stimuli underpinning CIBP signals is crucial for effective pain relief. This review aims to summarize the recent advances in studying the mechanisms of CIBP and explain the cellular and molecular mechanisms of CIBP at the level of the spinal cord.

CIBP After Bone Metastases

The main pathological mechanisms of CIBP include peripheral and central sensitization (Figure 1). The peripheral mechanisms mainly include bone tissue damage, changes in the local tumor microenvironment, and alterations in the DRG.

Due to the Warburg effect of tumor cells, even in the presence of sufficient oxygen, glucose tends to be converted to pyruvate, leading to lactate formation.⁹ This active metabolic reprogramming supports the biosynthetic requirement of sustained tumor proliferation, malignant progression, tumor microenvironment formation, and cell signaling.^{10,11} Blood flow in the bone marrow is abundant but slow. These characteristics provide a fertile environment for tumor cell growth, making it easy for tumor cells to attach to the bone surface and metastasize. In addition, the imbalance between the activity of osteoblasts and osteoclasts, stimulation of nerve fibers around bone, and the acidity of the environment further promote CIBP.^{7,12,13}

Once the tumor cells have implanted into bone to form bone metastases, an imbalance between osteoclast and osteoblast activity (that is, an imbalance between bone formation and bone resorption) occurs. Specifically, increased osteoclast function promotes the proliferation of tumor cells. Osteoclasts promote tumor cell survival under treatment with DNA damaging agents by producing glutamine.¹⁴ The secretion of interleukin(IL)-19, which binds to IL-receptor 20 subunit β (IL20RB) by osteoclasts promotes JAK1/STAT3 pathway activation in tumor cells expressing IL-20RB, thereby promoting tumor cell proliferation.¹⁵ In addition, after osteoclasts apoptosis during bone formation, a large number of apoptotic bodies are produced, which inhibit the activation of naïve CD8⁺T cells and promote cancer cell proliferation and spread.¹⁶ However, tumor cells also promote osteoclastogenesis by upregulating CUB-domain containing protein 1 expression on extracellular vesicles in the presence of receptor activator of nuclear factor(NF)- κ B ligand, culminating in vicious cycle.¹⁷ Therefore, studies and drug development attempts are underway to target the regulation of osteoclast function as an anti-tumor strategy, including research on colony stimulating factor-1 receptor, Siglec-15, and p38 mitogen activated protein kinase, amongst other osteoclast inhibitors.^{18–21}

Tumor cells also secrete neurotrophic factors/cytokines which promote the growth of nerve fiber axons and lead to perineural invasion (PNI), Sympathetic nerves promote cancer tumorigenesis and progression, while, parasympathetic and sensory nerves have anti-tumor effects.²² Neural fibers can also act on various immune cells in the tumor

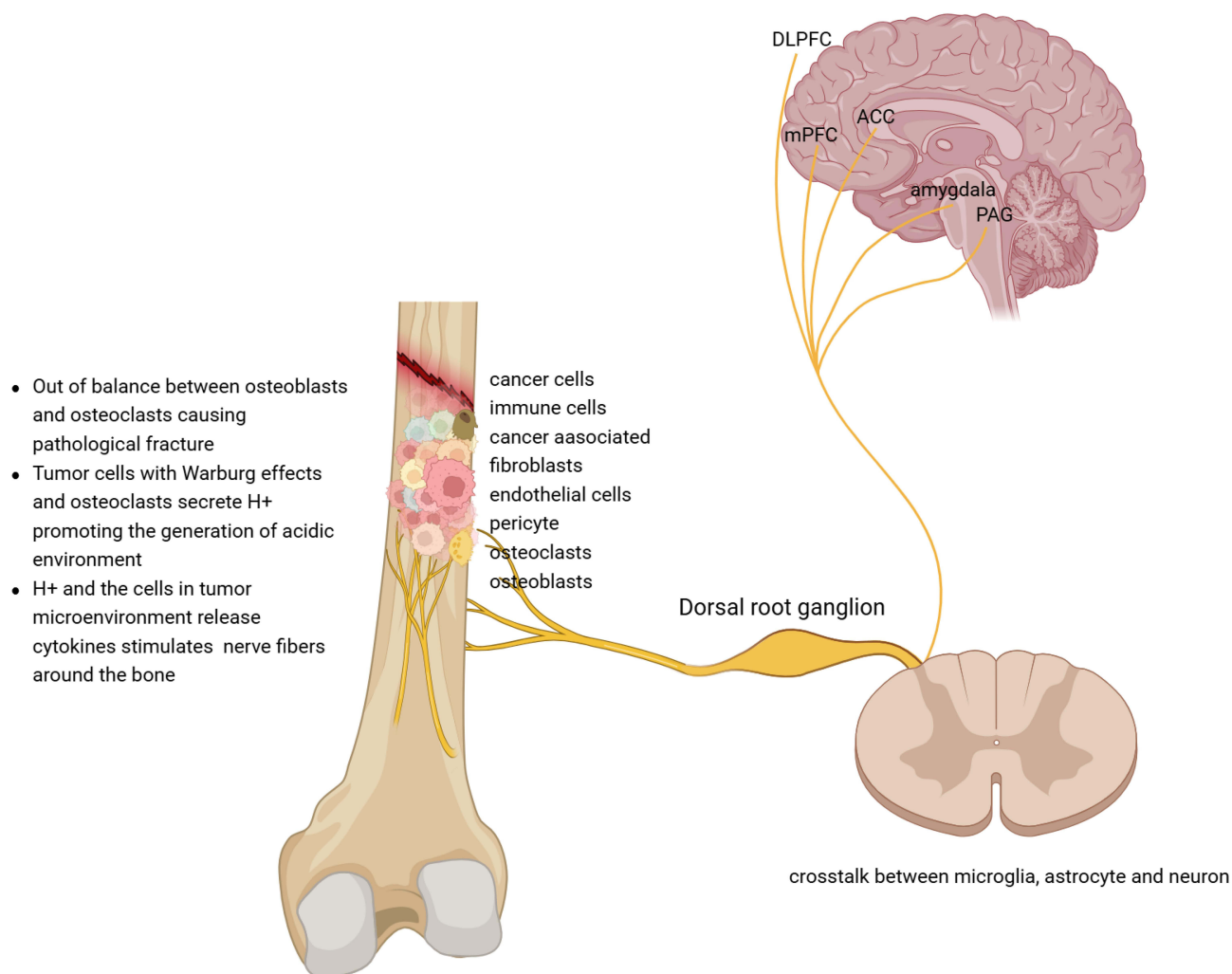


Figure 1 Mechanism of CIBP. Pathological fracture and cytokines in the tumor microenvironment stimulate nerve fibers. After peripheral injurious signals are transmitted into the spinal cord via the DRG, primary processing and integration of the information activates the relevant brain regions, leading to CIBP development. Created in BioRender. Tudou, T. (2024) <https://BioRender.com/y82r393>.

Abbreviations: CIBP, cancer-induced bone pain; DRG, dorsal root ganglion; DLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; PAG, periaqueductal gray.

microenvironment by releasing neurotransmitters. Therefore, the response of patients to immunotherapy can be predicted by evaluating PNI mediated inflammation.^{23–26}

The Warburg effect mentioned above and the increased expression of hypoxia-inducible factor- α in tumor cells increase, the production of protons (H⁺)/lactate ultimately leading to an acidic tumor microenvironment.^{27,28} In addition, tumor cells mediate tumor immunity and promote tumor progression by secreting high mobility group box 1 and nerve growth factor.^{29–32} These substances as well as H⁺ activate transient receptor potential channels, vanilloid subfamily member 1 (TRPV1),^{33,34} acid-sensing ion channel 3,³⁵ and the non-receptor tyrosine kinase Src,³⁶ thereby facilitating the conversion of chemical signals into electrical signals. The electrical signals are further transmitted to the spinal cord through the DRG, completing the first stage of signal transmission. The primary afferent nerve axons that transmit pain signals are myelinated A δ fibers and unmyelinated C fibers, with their neuronal bodies located in the DRG. The DRG also mediates the transmission of pain signals through TRPV1/TRPV4.^{37–39}

Spinal Mechanisms

Inflammatory pain is mainly caused by tissue damage or infection, while neuropathic pain is more related to nervous system damage or abnormal neuronal excitability. In addition to the characteristics of inflammatory

and pathological pain, CIBP also involves the interactions between tumor cells, bone cells, and immune cells, amongst other cell types. At the level of the spinal cord, neurons exhibit a decrease in the threshold for harmful stimuli, leading to central sensitization. However, the changes in spinal glial cells are not exactly the same between these types of pain. The central mechanisms underlying CIBP generally involve biochemical and electrophysiological changes in the spinal cord and brain. The spinal cord receives pain signals from the activation of nociceptive sensory neurons and is the primary center for pain signal processing and integration. Primary sensory neurons project to the spinal cord and brain stem through the DRG and trigeminal ganglia, while second order neurons project to the brain through the spinal cord, which mediates the sensation of pain. The spinal cord is a crucial connecting pathway between the brain and the peripheral nervous system.

Neuron-Glia Crosstalk

Microglia

Microglia and astrocytes are the main glial cell types in the CNS. The microglia are mainly distributed in the cortex of the brain, the cerebellum, and the gray matter of the spinal cord. They are the first immune cells to respond to CNS injury and are resident macrophages in the CNS. They participate in various immune responses together with infiltrating macrophages. Under pathological conditions, the microglia rapidly polarize into the M1 phenotype, releasing pro-inflammatory factors, such as IL-1 β and TNF- α , which participate in the sustained inflammatory response. Microglial polarization toward the M2 phenotype is believed to have anti-inflammatory effects, secreting various anti-inflammatory factors, including IL-10, growth factors, and neurotrophic mediators.^{40,41} Therefore, activated M1 microglia participate in pain induction and exist in parallel within pain response, while M2 microglia play an anti-inflammatory role and suppress pain.^{42,43} A previous study showed that in neuropathic pain, the microglia transition from the resting to the activated state, and inhibition of microglial activation attenuates hyperalgesia and allodynia.⁴⁴ However, the role of the microglia in CIBP is highly controversial.

A previous study showed that, in the spinal cord of a CIBP model, chemokine monocyte chemoattractant protein-1 stimulated the spinal microglia through activation of the PI3K/Akt pathway, and inhibiting this pathway alleviated CIBP.⁴⁵ The extracellular adenosine triphosphate (ATP)-gated channel P2X receptor (seven genes [*P2X1-P2X7*] encode P2X receptor subunits) is a non-selective cation channel that is permeable to sodium, potassium and calcium. The binding of ATP to the P2X receptor regulates opening and closing of the channel.⁴⁶ Activation of P2X4 and P2X7 receptors expressed by the spinal microglia damages the nervous system by promoting the release of pro-inflammatory factors (IL- β , TNF- α), ultimately leading to pain.^{47,48} In contrast, the P2Y receptor (eight genes [*P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, P2Y14*] encode the P2Y receptor subunits) is a G-protein-coupled receptor that is present in virtually all cells and that mediates inflammation and pain.⁴⁹ Activation of P2Y12 receptors expressed on the spinal cord microglia mediates CIBP development by promoting the secretion of pro-inflammatory factors (IL-1 β , IL-6, TNF- α).⁵⁰

Chemokines are cytokines that regulate the migration of immune cells, and the CXC chemokine family plays an important role in communication between tumor cells and their microenvironment, promoting angiogenesis, stimulating the inflammatory response, and facilitating tumor metastasis.^{51,52} In the spinal cord, microglia, astrocytes and neurons express CXCR4 and participate in CIBP production by activating downstream signaling pathways, including the ALK5/Smad3 signaling pathway, RhoA/ROCK2 pathway and CaMKII/CREB pathway.⁵³⁻⁵⁵ Therefore, it has been suggested that the inhibition of glial cell-derived proinflammatory factors, cell surface receptors, and intracellular signaling pathways may be beneficial for pain management in patients with terminal cancer.⁵⁶

Morphine is often used clinically in the terminal stage of cancer to relieve severe pain. However, patients who use morphine for a long period of time usually develop morphine tolerance. It has been found that pro-inflammatory factors, such as IL-1 β and TNF- α , which are secreted by M1 microglia, promote the development of morphine tolerance. Decreasing the secretion of these pro-inflammatory factors, increasing the secretion of anti-inflammatory factors (IL-10, TGF- β), and promoting the transition of M1 microglia to the M2-phenotype have been shown to inhibit morphine tolerance, contributing to morphine analgesia.⁵⁷ In addition, naringenin, which is mainly derived from citrus fruits, also has certain potential for treating cancer.⁵⁸ It inhibits TNF- α in peripheral bone tissues and serum, as well as promoting the polarization of M1 microglia to M2 microglia by activating the adenosine monophosphate-activated protein kinase/

peroxisome proliferator-activated receptor γ coactivator 1- α pathway. It is also a potential therapeutic drug for alleviating CIBP.^{59,60}

Although the above studies have shown that activation of the spinal microglia occurs in CIBP and facilitates the formation or maintenance of CIBP, other studies have suggested that CIBP is not associated with microglial activation. Some studies have shown that activation of the microglia is only observed in the early stages of CIBP modeling. It has also been demonstrated that inhibition of microglial activation does not alleviate CIBP. Another study showed that activation of the spinal microglia was not observed in male or female animals, but it was observed in the spare nerve injury model.^{61,62}

Therefore, studies regarding the involvement of the microglia in CIBP have produced contradictory results. The discrepancies may be related to whether tumor bone metastasis causes peripheral nerve damage or inflammatory changes. Moreover, the discrepancies may be related to the process used to model CIBP, the characteristics of different tumor cells, and variations in the responses of different animal species to tumor cells.

Astrocytes

In addition to the spinal microglia, astrocytes are an important source of inflammatory mediators and play a crucial role in chronic neuropathic pain.^{63,64} In non-pathological states, astrocytes provide metabolic support to neurons and maintain cellular homeostasis.⁶⁵ In the pain state, astrocytes participate in various processes related to persistent pain, and astrocyte activation usually follows microglial activation. After activation, astrocytes regulate the phenotype or function of the microglia by secreting various cytokines, and they continue to respond throughout the entire pathological pain period.⁶⁶ In the CIBP model, astrocytes activation precedes microglial activation.⁶⁷ Overall, the activation of reactive astrocytes plays an important role in the generation and maintenance of pain and is accompanied by changes in cell morphology, metabolism, and gene expression.⁶⁸ The proliferation of microglia differ, which means that they play different roles and exert varying effects under different pain conditions.⁶⁹ In the context of chronic pain, signaling molecules that change in activated astrocytes include cytokines, chemokines, ion channels, enzymes, and structural proteins.⁷⁰ These molecules participate in the activation of other signaling pathways, including cytokine signaling, JAK/STAT3 signaling, and kinase and protease signaling.⁷¹ They also suppress astrocyte-dependent signaling pathways, and neuroinflammation can alleviate mechanical and heat hypersensitivity in animals with CIBP.⁷² Proteinase activated receptor 2 (PAR-2) belongs to the G protein coupled receptor family and is widely expressed in mast cells, neurons, and astrocytes. It plays an important regulatory role in the occurrence and maintenance of different pathological pain states.⁷³ PAR-2 expressed after astrocyte activation also participates in the development of CIBP through the ERK/CREB pathway.⁷⁴ One study showed that in the CIBP model, NF- κ B not only increased in the microglia but it also increased in astrocytes and participated in CIBP development.⁷⁵ In addition, the functional changes that occur in the mitochondria of astrocytes have a certain impact on CIBP. Specifically, maintaining the dynamic balance between mitochondrial fusion and fission and reducing mitochondrial damage can alleviate CIBP.^{76,77} Meanwhile, inhibiting the reduction in mitochondrial membrane potential induced by pro-inflammatory cytokines also plays a role in alleviating CIBP.^{78–80} Astrocytes can also participate in cross-talk with neurons by releasing CXCL1 and CXCL12, which respectively act on CXCR2 and CXCR4 receptors on neurons.^{81–83} Figure 2 shows the molecular mechanisms that promote CIBP in the spinal cord through the activation of astrocyte-microglia, astrocyte-neuron and microglia-neuron interactions based on recently published studies.

It is worth noting that γ -aminobutyric acid (GABA) and its receptors are widely expressed in the nervous system and play an important role in the transmission and regulation of pain signals.⁸⁴ Studies have shown that GABA expression is reduced in the spinal cord of rats with CIBP due to cell apoptosis of GABAergic interneurons. The administration of exogenous GABA receptor agonists or ferroptosis inhibitors produces analgesic effects, and these agents exert their therapeutic potential via modulation of the neuron-glia interaction.^{85–87} It has also been shown that Sirtuin-2 expressed on spinal cord neurons induces CIBP by upregulating FoxO3a and antioxidant genes.⁸⁸

T Lymphocytes

The blood spinal cord barrier (BSCB) is mainly composed of capillary endothelial cells, basement membrane, pericytes, and astrocyte foot processes. Its main function is to restrict the infiltration of neuronal plasma components, blood cells, and pathogens

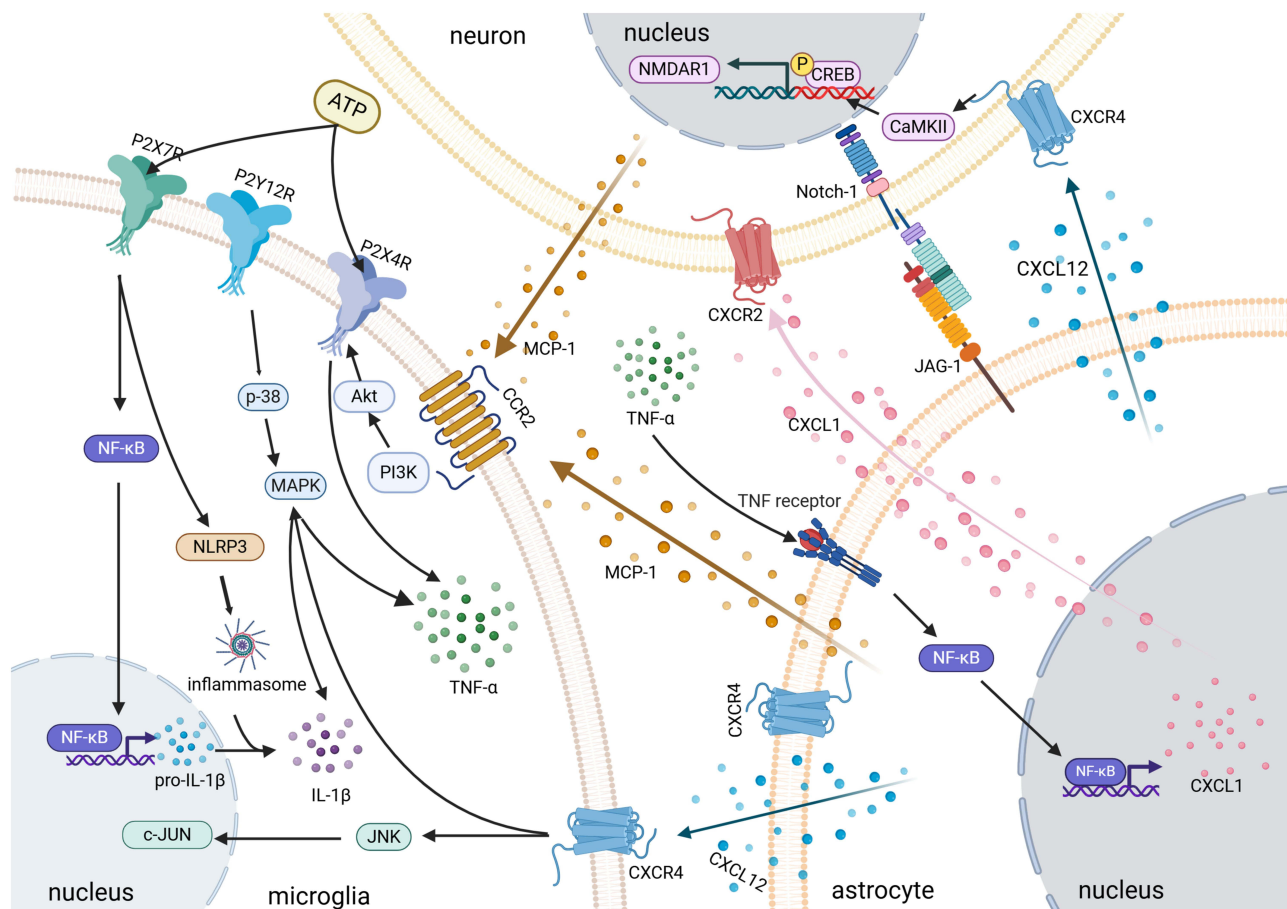


Figure 2 Crosstalk between the microglia, astrocytes, and neurons in the spinal cord. The microglia and astrocytes release pro-inflammatory factors or cytokines that act on the neurons, causing electrophysiological and biochemical changes within the neuron to facilitate nociceptive signaling. Neurons also communicate with the microglia and astrocytes through cytokines secretion and cell-to-cell interactions. Created in BioRender. Tudou, T. (2024) <https://BioRender.com/g54j188>.

from the blood into the spinal cord.⁸⁹ Pain models have demonstrated changes in BSCB permeability and increased infiltration of immune cells into the spinal cord.⁹⁰ One study used the Evans Blue extravasation assay to explore the changes in BSCB in a model of CIBP. The study showed that in the later stage of modeling, Evans Blue dye infiltration from the blood into the spinal cord continued to increase. The tight junctions between the endothelial cells were deformed and gaps were observed, indicating BSCB damaged.⁹¹ Transient BSCB injury appears in neuropathic pain, while long-term BSCB injury appears in CIBP, which may provide a basis for immune cell recruitment and infiltration. In the past, it was believed that peripheral immune cells could not enter the CNS. However, with further in-depth research on the relationship between lymphocytes and pain generation in the spinal cord, it has been gradually discovered that peripheral immune cells (especially CD3⁺T lymphocytes) entering the CNS promote the occurrence of nociceptive sensitization.⁹² In the maintenance of neuropathic pain, T cells infiltrate into the spinal cord, especially T helper type 17 (Th17) cells, which secrete pro-inflammatory factors, including IL-17 and TNF- γ ,⁹³ while regulatory T cells inhibit microglial activation and pain hypersensitivity in female mice. Intrathecal adoptive transfer of activated regulatory T cells modulates meningeal and peripheral immunity and glial cell activation, thereby alleviating neuropathic pain.^{94,95} A previous study showed that in a CIBP model, there was a pronounced infiltration of CD3⁺CD4⁺T cells in the spinal cord, with transient upregulation of regulatory T cells followed by an imbalance in Th17 cells.⁹⁶ Although studies have begun to reveal the role of spinal cord T cells in CIBP, there is still a limited understanding in this area of research.

The Role of Non-Coding RNA in the Spinal Cord in CIBP

It is generally believed that non-coding RNAs do not encode proteins, therefore, they are considered to have extremely limited effects. However, it has gradually been discovered that non-coding RNAs regulate neuroimmune communication

signals in the pain pathway by controlling macromolecular complexes in neurons, glial cells, and immune cells. MicroRNAs (miRNAs), in particular, play a very important role in the transmission of pain signals between spinal cord neurons and glial cells.⁹⁷ It has been extensively documented that the transmission of peripheral nociceptive signals to the spinal cord can cause changes in RNA levels in various cells, thereby mediating and regulating central sensitization. Although some non-coding RNAs do not encode proteins, they can still participate in the development of CIBP at the level of the spinal cord, especially circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs), which interact with miRNA sponges and regulate downstream signaling pathways.^{98,99} Many studies have shown that RNA changes in the spinal cord play an important role in modulating the release of pro-inflammatory cytokines, particularly in the context of inflammatory pain and neuropathic pain, by altering the activation status of glial cells and neurons,^{100–102} Therefore, some studies have suggested that targeting these RNAs can alleviate CIBP. Several key non-coding RNAs have been identified in animal models of CIBP, [Table 1](#) summarizes some animal studies on the roles of non-coding RNAs in the spinal cord in the context of CIBP in recent years.

Brain Mechanism

When peripheral nociceptive signals are transmitted from the periphery through the spinal cord to the brain and activate relevant brain regions, the sensation of pain is generated. However, there is no single brain region that is solely responsible for pain processing; rather, pain, results from the integration of information from multiple brain regions. Previous studies have shown that the dorsal lateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), secondary somatic cortex (SII), and amygdala are significantly activated in patients with CIBP, and the functional connectivity between the right DLPFC and ACC is positively correlated with the duration of cancer pain. The functional connectivity between the left ACC and amygdala contributes to pain aversion, and the functional connectivity between the left SII and right SII is also enhanced. The SII is mainly involved in pain perception, and these brain regions play

Table 1 RNA and Related Signal Pathway in Spinal Cord of CIBP Model

Authors/Year	Locations	Methods of animal model established	RNA and related signal pathway	Ref
Liu, M. et al 2021	Astrocyte	Osteolytic sarcoma cells injected into the femur of male C3H/HeJ mice	miR-135-5p, JAK2/STAT3	[94]
Liu, C. et al 2020	Spinal cord	Walker 256 breast carcinoma cells injected into the tibia of female Wistar rats	miR-300, HMGB1	[95]
Saadh, M. J. et al 2023	Astrocyte	Osteolytic sarcoma cells NCTC 2472 injected into the femur of male C3H/HeJ mice	miR-199a-3p, MyD88/NF-κB	[96]
Kuang, J. et al 2023	Neuron	MADB 106 cells injected into female Sprague-Dawley (SD) rats	miR-199a-3p, DNMT3a/Nrf2	[97]
Zhang, Z. et al 2020	Spinal cord	Osteolytic 2472 sarcoma cells injected into the femur of male C3H/HeJ mice	circRNA-9119, miR-26a, TLR3	[98]
Wu, X. P. et al 2019	Microglia	Murine breast tumor (4T1 cell) cells injected into the tibia of female C3H/HeJ mice	miR-329, LPAR1/ERK	[99]
Jian, Y. et al 2022	Microglia	Walker 256 breast carcinoma cells injected into the tibia of female Sprague Dawley (SD) rats	miR-155-5p, SGK3	[100]
He, Q. et al 2022	Neurons	Walker 256 tumor cells injected into the tibia of female adult SD rats	miR-155-5p, TCF4	[101]
Ni, H. et al 2023	Spinal cord	Walker 256 cells injected into female Sprague Dawley rats tibial	LncRNA71132, miR-143-5p, GPR85	[102]
Chen, J. et al 2022	Neurons	Walker 256 cells injected into Sprague Dawley female rats tibial	NONRATT009773.2, miR-708-5p, CXCL13	[103]
Wang, A. et al 2020	Spinal cord	Osteosarcoma NCTC 2472 cells injected into male C3H/HeJ mice, femur cancer pain model	miR-184, CX3CR1	[104]
Hou, B. et al 2016	Spinal cord	Osteosarcoma NCTC 2472 cells injected into the femur of male C3H/HeNcrlVr mice	miR-132, CREB/CRTC1	[105]

important roles in pain management in CIBP.^{103,104} In addition, during CIBP, hyperpolarization activated cyclic nucleotide gated 1 (HCN1) and HCN2 channels on periaqueductal gray (PAG) neurons significantly increase, participating in CIBP development.¹⁰⁵ Stimulator of interference genes (STING) are key signaling molecules involved in the innate immune response, which can be triggered by exogenous DNA. STING activate the TBK1 and NF- κ B signaling pathways in the median prefrontal cortex and participate in CIBP development by promoting M1 polarization of the microglia.¹⁰⁶ However, study showed that STING agonists can inhibit cancer-induced osteoclastogenesis and bone destruction when administered systemically through type-I interactions, ultimately alleviating CIBP¹⁰⁷

Treatments for CIBP

Although many studies have evaluated the mechanisms of CIBP development, experimental results have varied owing to differences in tumor cell lines, animal types, and other aspects. Therefore, these models do not fully simulate the pain state of patients with cancer. Most studies are currently limited to preclinical animal experiments, with few clinical research reports. Medications, such as denosumab,¹⁰⁸ can reduce bone destruction. Moreover, bisphosphonates can reduce the activation of acid-sensing channels,¹⁰⁹ making it a useful treatment for CIBP. However, opioid drugs are still the main treatment method for patients with advanced CIBP in clinical practice, which may be supplemented by other physical or pharmacological therapies.

The three-step pain management ladder guidelines released by the World Health Organization have always been the “gold standard” for cancer pain management. The aim is to gradually use non-opioid analgesics, weak opioid drugs, and finally strong opioid drugs according to each patient’s pain intensity, and other auxiliary analgesics or symptomatic treatments can be integrated into the above treatment approach.¹¹⁰ Subsequent, studies have suggested adding two additional steps to this treatment approach. The fourth step considers that if the side effects of strong opioid drugs are treated, and the patient still obtains less than 30% pain relief within 24 hours, or if the patient experiences side effects such as confusion, hallucinations, drowsiness, or dry mouth, it is necessary to switch to another opioid drug or change the administration route to improve the analgesic effect and reduce adverse reactions. If the patient still does not achieve therapeutic benefit, anesthesia intervention may be considered.¹¹¹ In addition, studies have shown that the combination of acupuncture therapy and the three-step analgesic drug therapy published by the World Health Organization can achieve better analgesic effects, with which the incidence of adverse reactions, such as nausea and vomiting, is lower.¹¹² In addition, an important treatment concept is individualized of therapy, as each individual has a different response to medication. Opioid drugs are the main methods to relieve CIBP, however, their side effects, such as constipation, cannot be ignored. The Edmonton Classification System for Cancer Pain composite score can also be applied to assist in implementing individualized interventions and therapy for CIBP.¹¹³ Patients may also need psychological or non-pharmacological treatments, including acupuncture or massage.^{114–116} Comprehensive and personalized analgesic treatment is beneficial for patients to achieve a better quality of life in the later stages of CIBP.

Future Directions and Conclusions

CIBP is a pain state in which patients with cancer experience persistent or explosive pain. Although there are various drugs available for the treatment of CIBP in clinical practice, the pain of experienced by patients with CIBP cannot be completely relieved, and the analgesic effects of commonly used opioid drugs are limited. Patients treated with opioids are prone to tolerance and drug-related side effects, which seriously affect their quality of life. Therefore, it is extremely important to explore the mechanisms of CIBP in depth. In patients with late-stage cancer bone metastasis, metastasis and tumor spread, as well as deterioration of the condition, are irreversible. Therefore, maximizing analgesia and minimizing side effects should be the focus of treatment for CIBP, with the goal of improving quality of life. At present, the treatment of CIBP is mostly based on the symptoms of pain rather than cancer related pain itself. Therefore, understanding the changes that occur in CIBP at the level of the spinal cord is beneficial for improving the clinical treatment of patients with this condition. The communication between the spinal microglia, astrocytes, and neurons has been widely studied in the context of CIBP. With the continuous deepening of research, the role of T-cell infiltration into the spinal cord has gradually become a topic of research interest. However, further research in this field is still needed. Although many

studies have identified potential therapeutic targets and explored novel analgesic drugs for CIBP, most treatment methods still lack clinical translational value and do not achieve significant pain relief or quality of life improvement.

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Disclosure

The authors report no conflicts of interest in this work.

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